HCV AND THE KIDNEY UNFOLDING THE CHALLENGES

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AGENDA

- A look at the past
- Treatment of HCV patients
- Treatment Guidelines of HCV in renal patients
- Treatment of cryoglobulinemic HCV nephropathy
- Treatment of HCV after kidney transplantation

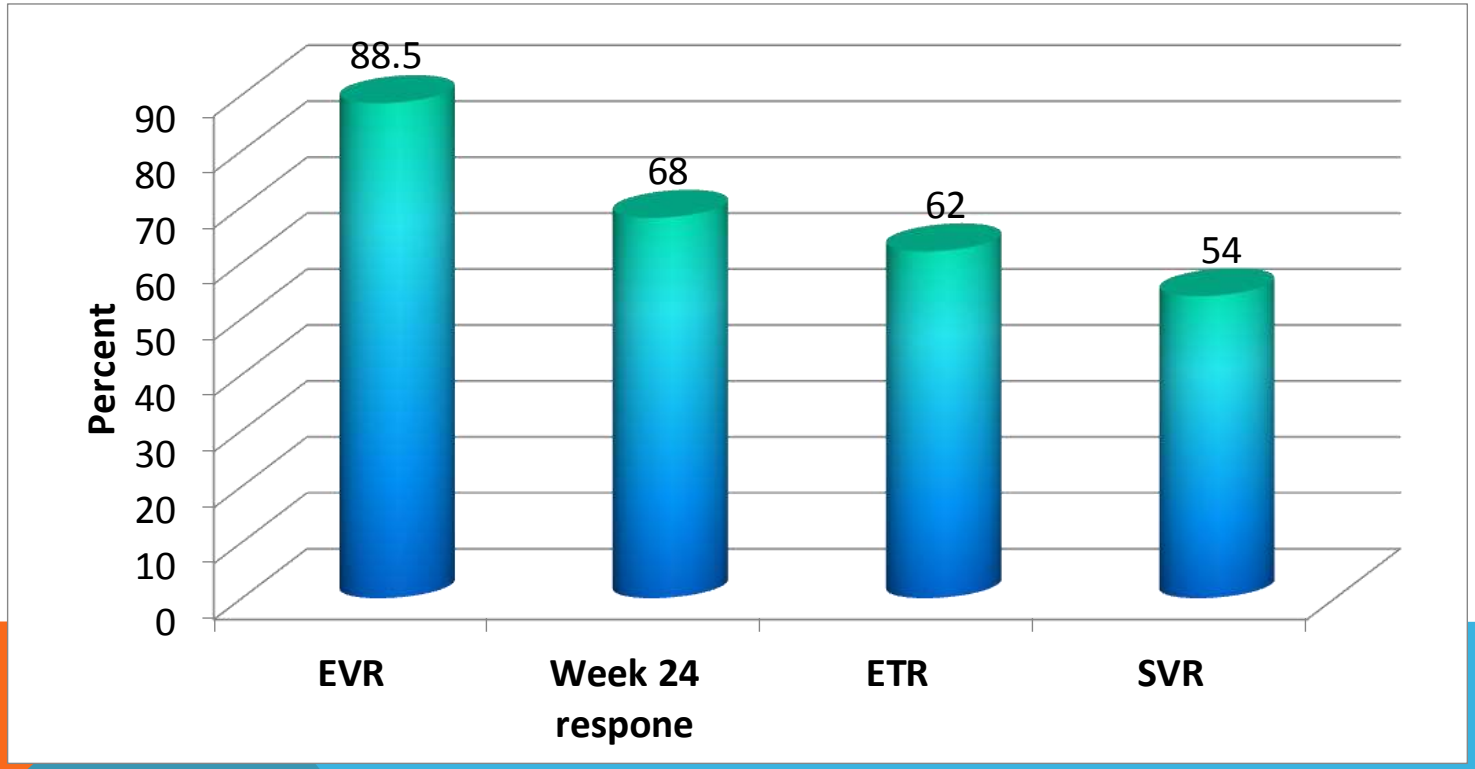
A look at the past

A LOOK AT THE PAST

Ministry of Health, Egypt

National Committee for Control of Viral Hepatitis

National HCV Treatment Program

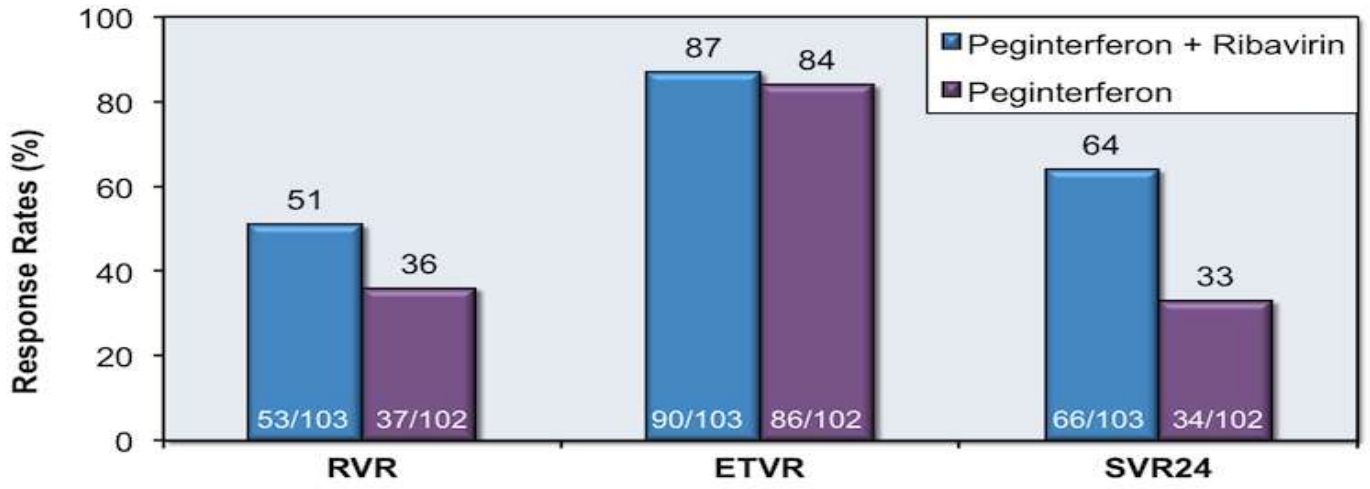


RESPONSE RATES OF TREATED PATIENTS

A LOOK AT THE PAST

Stages of CKD	IFN[a]	Ribavirin[b]
1 and 2	Pegylated IFNα-2a: 180 µg SQ q wk Pegylated IFNα-2b: 1.5 µg/kg SQ q wk	800–1200 mg/d in two divided doses
3 and 4	Pegylated IFNα-2a: 135 µg SQ q wk Pegylated IFNα-2b: 1 µg/kg SQ q wk	*
5	Pegylated IFNα-2a: 135 µg SQ q wk Pegylated IFNα-2b: 1 µg/kg SQ q wk	*

Genotype 1: Virologic Responses



Treatment of HCV patients

TREATMENT REGIMENS

Treatment recommendations for HCV-monoinfected (F0-F3) including:

(a) Treatment-naïve patients

(b) Patients who failed on a treatment based on Peg-IFN-α & ribavirin (RBV).

Regimen	Sofosbuvir +Daclatasvir	Sofosbuvir +Ledipasvir	Ritonavir +Paritaprevir +Ombitasvir +RBV	Sofosbuvir +Simeprevir	Sofosbuvir +RBV	PEG-IFNα +RBV +Sofosbuvir
Duration	12w	12w	12w	12w	24w	12w

Treatment recommendations for compensated (Child-Pugh A) cirrhosis (F4) including:

(a) Treatment-naïve patients

(b) Patients who failed on a treatment based on Peg-IFN-α and ribavirin (RBV).

Regimen	Sofosbuvir +Daclatasvir	Sofosbuvir +Ledipasvir	Ritonavir +Paritaprevir +Ombitasvir +RBV	Sofosbuvir +Simeprevir	Sofosbuvir +RBV	PEG-IFNα +RBV +Sofosbuvir
Duration	+RBV-12w -RBV 24w	+RBV-12w -RBV 24w*	24 w	+RBV-12w Naive or relapser -RBV 24w* Null or partial responder	24w	12w

Treatment of relapser patient
(To sofosbuvir based therapy either SOFO+RBV or PEG-IFN +SOFO+RBV)

	Sofosbuvir +Ledipasvir	Sofosbuvir +Daclatasvir	Sofosbuvir +Simeprevir	Ritonavir +Paritprevir +Ombitasvir
	With RBV			
F0-2	12w	12w	12w	12 w
F3-4	24w	24w	24w	24w

Guidelines

CrossMark

EASL | JOURNAL OF HEPATOLOGY

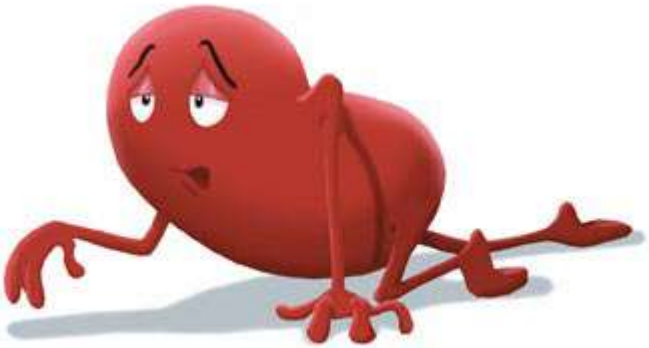
EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver*

	Paritprevir 150mg +Ombitasvir 25mg +Ritonavir 100mg	Elbasvir 50 mg+ Grazoprevir 100mg	Ledipasvir 90mg+ Sofosbuvir 400mg
F0-3	12 weeks	12 weeks	12 weeks
Ribavirin	Weight based	-	-
Class Level	I A	II a B	II a B
F4	12 weeks	12 weeks	12 weeks
Class Level	I B	II a B	II a B

Updated: February 24, 2016. Changes made: March 10, 2016.

Treatment guidelines of HCV in renal patients



HCV with renal impairment

Mild to moderate renal impairment (creatinine clearance 30-80 ml/ min).

No dosage adjustment is required when using

1	2	3	4
• Daclatasvir • Sofosbuvir	• Ledipasvir • sofosbuvir	• Paritaprevir • Ritonavir • Ombitasvir	• Simeprevir • sofosbuvir

Class I, level A

HCV with renal impairment

HCV Patient Genotype 4 with:

1. Creatinine clearance < 30 ml/min
2. Do not have cirrhosis
3. Urgency to treat or retreat is high.
4. Renal transplant is not an immediate option.

N.B. Limited data exist with this regimen in patients with renal failure.

Class II b, level B

1	2	3	4
• Daclatasvir • Sofosbuvir	• Ledipasvir • sofosbuvir	• Paritaprevir • Ritonavir • Ombitasvir	• Simeprevir • sofosbuvir

Paritprevir 150mg +Ombitasvir 25mg +Ritonavir 100mg

- AM dosing 2 tablets.
- Take with food.
- No dose adjustment is required with mild hepatic impairment or mild, moderate or severe renal impairment .

The safety and efficacy of Qurevo has not been established in HCV patients with moderate hepatic impairment (Child Pugh B).

Qurevo is Contra indicated in patients with severe hepatic impairment (Child Pugh C).

GRAZOPREVIR AND ELBASVIR

Grazoprevir and Elbasvir (Investigational): In C-SURFER, a phase 2/3 trial

Patients with chronic HCV genotype 1 and advanced renal disease (stage 4 or 5), investigators reported findings using a 12-week course of the investigational agents grazoprevir and elbasvir.

Enrollment included treatment-naive patients (83%) and treatment experienced patients (17%) who had failed a peginterferon-based regimen.

Overall, 115 (99%) of 116 patients treated achieved an SVR12.

Patients with Severe Renal Impairment (CrCl less than 30 mL/min) or End-Stage Renal Disease

Genotype 1a: The recommended regimen is standard dose ombitasvir-paritaprevir-ritonavir and dasabuvir in combination with reduced-dose ribavirin (200 mg three times weekly to 200 mg once daily).

Genotype 1b: The recommended regimen is standard dose ombitasvir-paritaprevir-ritonavir plus dasabuvir (limited data in patients with renal failure).

Genotype 2: The recommended regimen is PEG-IFN plus dose-adjusted ribavirin.

Genotype 3: The recommended regimen is PEG-IFN plus dose-adjusted ribavirin.

Genotype 5 or 6: The recommended regimen is PEG-IFN plus dose-adjusted ribavirin.

Patients with Severe Renal Impairment (CrCl less than 30 mL/min) or ESRD

Peginterferon Dosing: In patients with severe renal insufficiency, including those with end- stage renal disease, the dose of peginterferon alfa-2a should be reduced to 135 mcq once weekly and the dose of peginterferon alfa-2b should be reduced by 50% (to 1.0 mcg/kg once weekly).

Patients with Severe Renal Impairment (CrCl less than 30 mL/min) or End-Stage Renal Disease

Ribavirin Dosing: The recommended ribavirin dose with severe renal disease, including end stage renal disease is 200 mg/day.

Most experts recommend starting the dose at 200 mg three times weekly and titrating up to 200 mg/day as tolerated. Caution should be exerted when using ribavirin in patients with renal failure because of the risk of severe hemolysis.

In addition, ribavirin use should be restricted to patients who have a baseline hemoglobin greater than 10 g/dL and it should be discontinued if the hemoglobin level decreases by more than 2 g/dL despite the use of erythropoietin.

Patients who are Ribavirin Intolerant or Ineligible to Receive Ribavirin: In this situation, expert consultation is recommended to evaluate for possible use of a sofosbuvir containing regimen.

Liver INTERNATIONAL

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RAPID COMMUNICATION

Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series

Tavankit Singh[1,*], John Guirguis[2,*], Sumi Anthony[2], John Rivas[2], Ibrahim A. Hanouneh[2] and Naim Alkhouri[2,3]

8 patients with chronic HCV infection on hemodialysis

Treated with sofosbuvir- simeprevir or sofosbuvir- ledipasvir

The mean eGFR was <30ml/min. The mean serum creatinine and serum blood urea nitrogen (BUN) levels were 5.8 ± 2.7 mg/dl and 49.5 ± 10 mg/dl .

One patient each developed uncontrolled nausea and vomiting, headache, insomnia and a drop in hemoglobin of >2g/dl.

100%
SVR 12

The levels of sofosbuvir and GS-331007 were not measured

Received 14 November 2015; Accepted 20 January 2016

Pharmacokinetics of sofosbuvir 200mg vs. 400 mg in ESRD

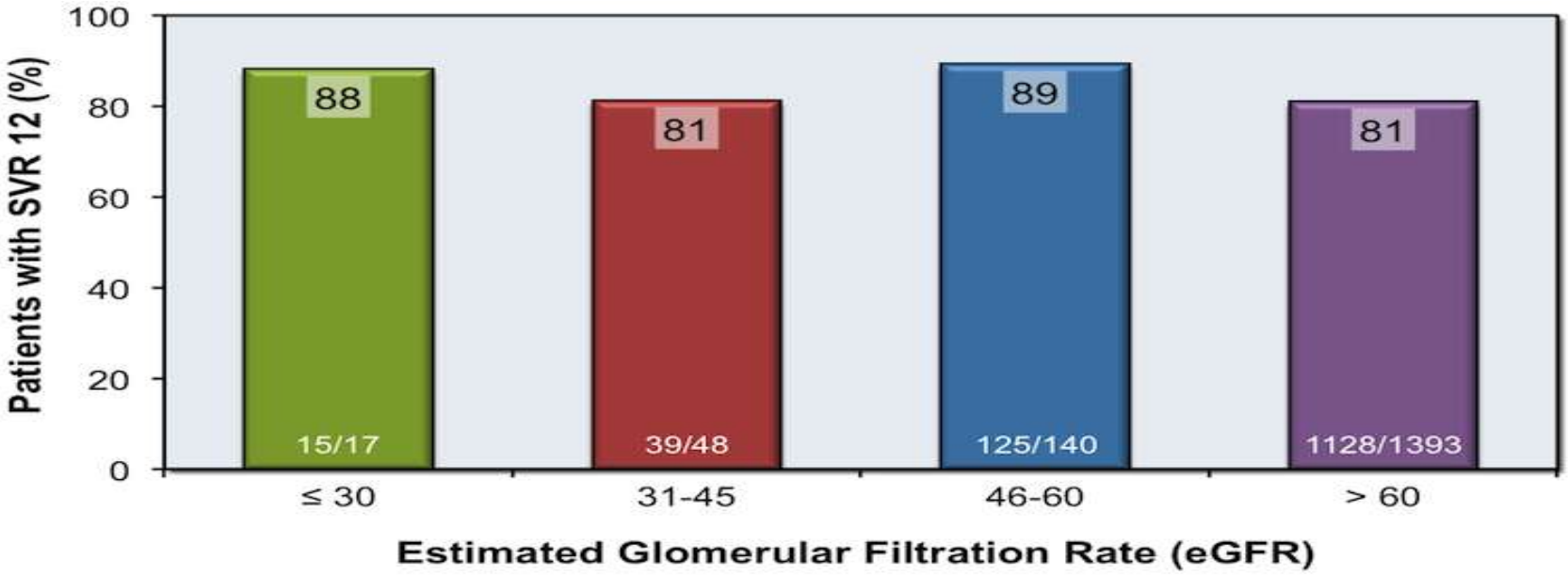
	Setting	Sofosbuvir AUC	GS-331007
Sofosbuvir 400mg	Severe CKD	171%	451%
	1 h pre-HD	28%	1280%
	1 h post-HD	60%	2070%
Sofosbuvir 200 mg	Severe CKD	5-10%	300%
	1 h pre-HD	NA	NA
	1 h post-HD	NA	NA

HCV Target : SVR 12 by eGFR

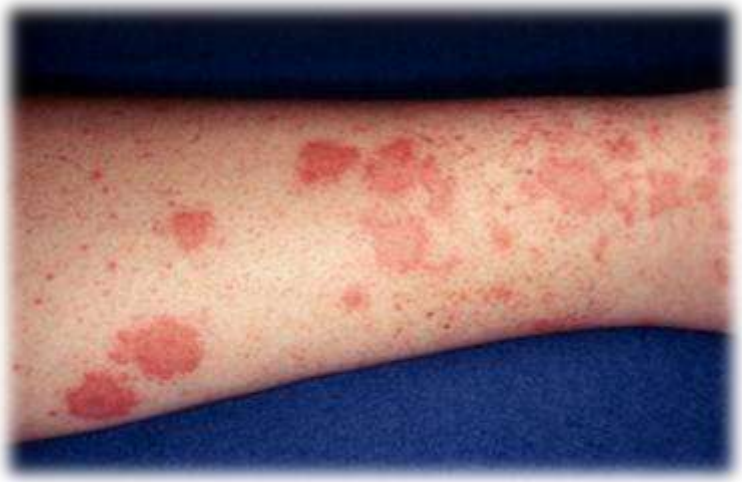
Longitudinal cohort study of 1893 patients using one of four sofosbuvir-containing regimens:

(1) Sofosbuvir plus peginterferon plus ribavirin.
(2) Sofosbuvir plus ribavirin.
(3) Sofosbuvir plus simeprevir.
(4) Sofosbuvir plus simeprevir plus ribavirin.

Overall, the SVR12 rates were high (81 to 89%) across different levels of baseline renal insufficiency with the one exception that cirrhotic patients with estimated GFR less than 30 ml/min/1.73m^2 had lower SVR12 rates.



Treatment of cryoglobulinemic HCV nephropathy



Treatment of cryoglobulinemic HCV nephropathy

HCV ab (third generation ELISA test is more specific and sensitive).

Assessment of viral load by RT-PCR.

ALT assessment (in 70%).

S. complement C1q, C4, C3.

Cryoglobuin, RF (70%), ANA (17–41%), ACL (20–27%), ASMA (9–40%) and ATG (8–13%).

Urine analysis:

Presence of proteinuria

Microscopic haematuria

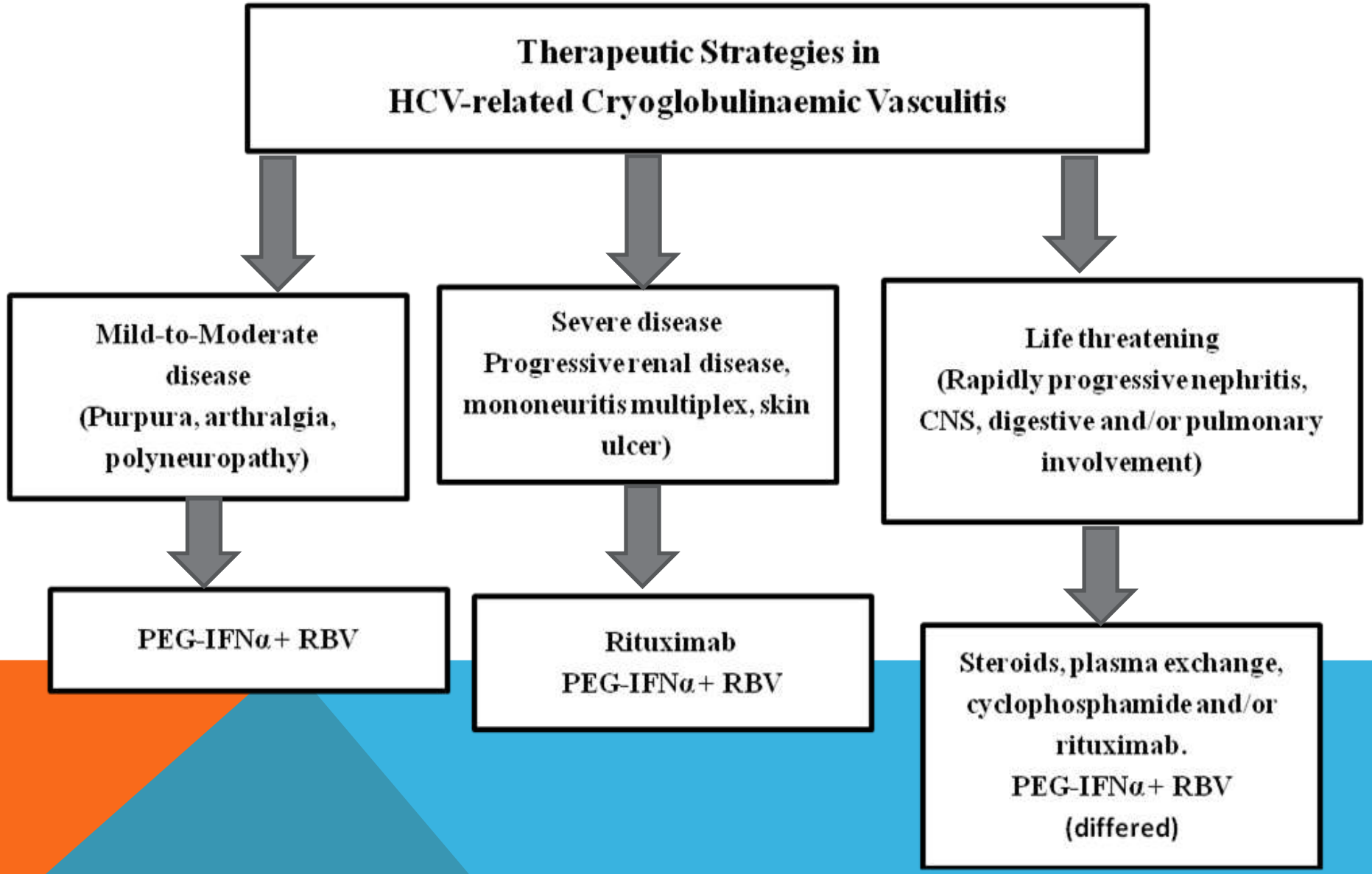
± impaired kidney function

Majority of patients develop severe HTN not respond to ttt

Renal biopsy: MPGN with typical immune complex deposition in glomeruli

Liver biopsy provides key information .

Therapeutic strategies in HCV-MC vasculitis



(Saadoun et al., 2007).

Therapy of HCV associated MC-GN *(Fabrizi et al., 2008)*

Nephrotic-range proteinuria and/or rapidly progressive kidney failure and/or acute flare of cryoglobulinemia	i) <u>Phase 1</u> ➢ Corticosteroid therapy: i.v. MP boluses (0.5-1 g/d on 3 consecutive days) + oral CCS (0.5 mg/kg/d slowly tapered to 0.1-0.2 mg/kg/d for 4-6 months) ➢ Oral cyclophosphamide (1-2 mg/kg/d for 2-4 months) ➢ Plasma exchange (exchanges of 2-3 L plasma x3/week for 2-3 weeks) ➢ Rituximab IV (375 mg/m^2/w for 4 weeks) After control of vasculitic syndrome has been achieved: <u>ii) Phase 2</u> ➢ Antiviral therapy

Treatment of cryoglobulinemic HCV nephropathy

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Treatment of Hepatitis C Virus–Associated Mixed Cryoglobulinemia with Direct-Acting Antiviral Agents

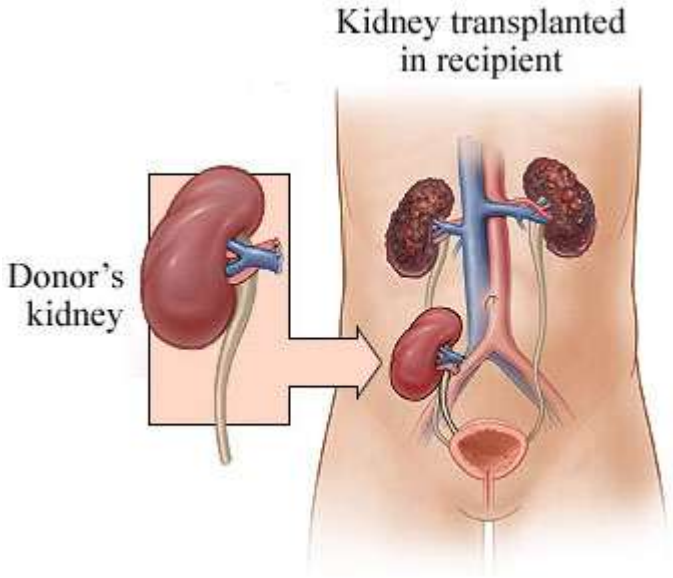
Meghan E. Sise,[1] Allyson K. Bloom,[2] Jessica Wisocky,[3] Ming V. Lin,[4] Jenna L. Gustafson,[3] Andrew L. Lundquist,[1] David Steele,[1] Michael Thiim,[3] Winfred W. Williams,[1] Nikroo Hashemi,[4] Arthur Y. Kim,[2] Ravi Thadhani,[1] and Raymond T. Chung[3]

HEPATOLOGY, Vol. 63, No. 2, 2016

Treatment of cryoglobulinemic HCV nephropathy (no 7/12)

	1	2	3	4	5	6	7
Age/sex	59/M	73/F	52/M	58/M	59/F	60/M	69/M
Cirrhosis	No	Yes	No	Yes	Yes	No	Yes
Prior antiviral ttt	None	Intolerant of IFN/RBV	None	Relapser on TLV/IFN/RBV	Intolerant of IFN/RBV	Intolerant to IFN	None
ANA titer	1/40	1/5210	negative	negative	1/40	ND	1/160
C3-C4	Low	Low	Normal	Low	Normal	ND	Low
Cryoglobulin	4%	2%	1%	3%	0.5%	2%	1%
RF	+ve	+ve	+ve	+ve	ND	+ve	-ve
Immuno-suppression							
prior to ttt	CS, RTX	RTX	None	RTX	CS, RTX	Phersis, RTX	RTX, Usekinumab
Concurrent	RTX	--------	---------	---------	--------	----------	Usekinumab
After ttt	-----	-------	---------	---------	---------	-------	usekinuma
Regimen	SOF/SIM	SOF/SIM	SOF/RBV	SOF/SIM	SOF/SIM	SOF/SIM	SOF/SIM
SVR	Yes	yes	yes	yes	yes	yes	No

Treatment of HCV after kidney transplantation



Treatment of HCV after kidney transplantation

HCV infection is common in kidney transplant recipients. It is responsible for :

(A) Decreased survival of patients and kidney allografts.

(B) Increased liver fibrosis.

(C) Increased infection rates.

(D) New-onset diabetes mellitus.

(E) Cardiovascular disease.

(Kamar et al., 2015)
American J Transplantation

Treatment of HCV after kidney transplantation

Until now, there has been no efficient and safe therapy to eliminate HCV infection after kidney transplantation. Indeed, interferon-a is relatively contraindicated because of an increased risk of acute rejection due to its immunostimulatory properties.

It can be considered in case of severe cholestatic hepatitis or progressive/advanced fibrosis.

Ribavirin as a monotherapy, amantadine as a monotherapy, or a combination of both do not have any impact on HCV viral load.

In the post-transplantation setting, patients typically have good recovery of renal function, and use of new directly acting antiviral agents may provide excellent interferon-free treatment options.

American Journal of Transplantation 2015; XX: 1–6
Wiley Periodicals Inc.

doi: 10.1111/ajt.13518

Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation

Indications:

1. Advanced fibrosis by METAVIR Score F3 or F4 [n=11].
2. Patients at high risk of graft loss (i.e. Hx of kidney function loss due to HCV-induced membranoproliferative glomerulonephritis [n=7].
3. Concomitant proteinuria and cryoglobulinemia [n=6]
4. Active HCV-related non-renal cryoglobulinemic manifestations [n=1].

Exclusion criteria:

None of these patients had decompensated cirrhosis.

Total number= 25

American Journal of Transplantation 2015; XX: 1–6
Wiley Periodicals Inc.

doi: 10.1111/ajt.13518

Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation

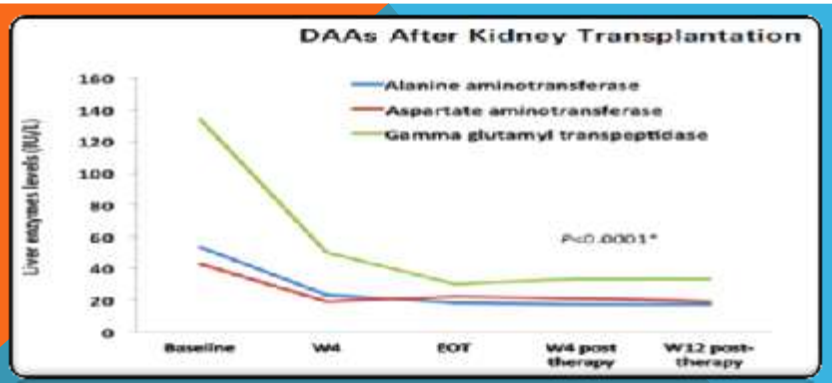
HCV genotype	N	DAA combination	Duration (wk)
1a	2	Sofosbuvir + ledipasvir	12
	1	Pegylated interferon + ribavirin + sofosbuvir	24
	1	Sofosbuvir + simeprevir	12
1b	5	Sofosbuvir + simeprevir	12
	5	Sofosbuvir + ledipasvir	12
	3	Sofosbuvir + daclatasvir	24
	1	Sofosbuvir + ledipasvir + ribavirin	24
	1	Sofosbuvir + simeprevir + ribavirin	12
2	2	Sofosbuvir + ribavirin	12
3	1	Sofosbuvir + ribavirin	24
4	2	Sofosbuvir + ledipasvir	12
	1	Sofosbuvir + daclatasvir	12

American Journal of Transplantation 2015; XX: 1–6
Wiley Periodicals Inc.

doi: 10.1111/ajt.13518

Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation

	Base line	Week 4	ETR	4 Weeks post ttt	12 weeks post ttt
GRR (ml/m)	61±21	58±21	58±18	59±20	59±20
S. creatinine	117±57	118±65	125±67	128±71	126±69
Cryoglobulin mg/l	52 (44-476)				27.5 (0-141)
Albuminuria mg /daily	224 (57-600)				200 (20-749)



SVR 12 100%

DAA INTERACTIONS WITH CALCINEURIN INHIBITORS

	Cyclosporine	Tacrolimus
Sofosbuvir	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Ledipasvir	No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Daclatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Simeprevir	5.81-fold ↑ in SIM AUC; combination is not recommended	85% ↑ in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
PrOD	5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
PrO	4.3-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed	86-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed

Treatment of HCV after Post kidney transplantation

A phase 2 international trial is underway with ledipasvir-sofosbuvir given for 12 or 24 weeks in kidney transplantation recipients with chronic HCV genotype 1 or 4 infection. The use of the regimen ombitasvir-paritaprevir-ritonavir and dasabuvir also has potential for use in the post renal transplant setting, but the ritonavir cytochrome p450 inhibition is potentially significant and may require cyclosporine or tacrolimus dose adjustments.

In addition, the combination of daclatasvir and sofosbuvir may provide an option in the post-transplantation setting.

Treatment of HCV infection post-liver transplantation

Regimen	Duration	Fibrosis stage	Type of patient	Rating
Ledipasvir 90mg + Sofosbuvir 400mg +weight base RBV	12 wks	Including compensated cirrhosis	Naïve Experienced	Class I Level A
Daclatasvir 60mg +Sofosbuvir 400mg + initial dose RBV 600mg	12 wks			Class I Level B
Ledipasvir 90mg + Sofosbuvir 400mg	24 wks		Intolerant or ineligible to RBV	Class I Level B
Daclatasvir 60mg +Sofosbuvir 400mg	24 wks			Class II Level C
Ledipasvir 90mg + Sofosbuvir 400mg +low initial dose of RBV (600 mg, increased as tolerated)	12 wks	Decompensated cirrhosis (CTP class B or C)	Naïve Experienced	Class I Level B
Daclatasvir 60mg +Sofosbuvir 400mg	24 Wks			Class II b Level C

HOME MESSAGES

No dosage adjustment is required in presence of mild to moderate renal impairment (creatinine clearance 30-80 ml/ min).

When creatinine clearance is < 30 ml/min, patient do not have cirrhosis, urgency to treat or retreat is high and renal transplant is not an immediate option, fixed daily dose of paritprevir 150mg, ombitasvir 25mg and ritonavir 100mg is the target drug.

The tolerance to the sofosbuvir-based therapy was excellent in kidney transplant recipients. there was no significant change in kidney function, and there were no acute rejections or graft losses.

Monitor immunosuppressive drug levels and found no significant change in the dose of immunosuppressive drug that was needed during sofosbuvir therapy, including simeprevir (a protease inhibitor). However, after HCV clearance, there was a decrease in tacrolimus trough levels, whereas tacrolimus dose remained unchanged.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